Remarks

Entry of the following response, as well as reconsideration and withdrawal of the rejections of record, is respectfully requested.

Summary of Status of Amendment and Office Action

In the present amendment, no claim is cancelled, claims 8-10 are amended, and no claim is added. Therefore, claims 8-26 remain pending in the application.

In the Office Action dated July 2, 2007, claims 8-12, 16 and 17 are rejected under 35 U.S.C. § 103 (a) as obvious in view of Fahrig et al. (WO 96/23506, Abstract only).

Additionally, claims 8-26 are rejected under 35 U.S.C. § 112, second paragraph as indefinite.

Response to Rejection of Claims 8-26 as Indefinite

The Office Action rejects claims 8-26, asserting that the term "protected form" recited in claims 8-10 is indefinite.

In response, claims 8-10 have been amended to delete the term "protected form," rendering the rejection moot. Reconsideration and withdrawal of this rejection is requested.

Moreover, because this was the only ground of rejection for claims 13-15 and 18-26, it is respectfully submitted that these claims are allowable upon withdrawal of this ground of rejection.

Regarding the amendment, it is noted, that the term "protected form" is merely another way of stating the equivalent term "prodrug." It is respectfully submitted that the term "protected form" is more often used by chemists, and that the term "prodrug" is more often used

by clinicians. However, the person of ordinary skill in the art reading the disclosure would understand the two terms to mean the same thing.

Accordingly, because claims 8-10 have been amended merely to remove a redundant term, the amendment does not have any affect on the scope of the amended claims, or on claims that depend from them. Moreover, the amendments have not been made to overcome the prior art. Accordingly, no estoppel should be deemed to attach thereto.

Response to Rejection of Claims 8-12, 16 and 17 as Obvious

Claims 8-12, 16 and 17 are rejected under 35 U.S.C. § 103 (a) as obvious in view of Fahrig et al. (WO 96/23506, Abstract only). The Office Action asserts that the Fahrig Abstract discloses 5' substituted in combination with at least one cytostatic to prevent or reduce build-up of resistance in cytostatic treatment, and also discloses a medicament containing BVDU and/or its metabolites. It is the position in the rejection that since the Fahrig Abstract discloses that BVDU and/or its metabolites can reduce build-up of resistance in cytostatic treatment, it would have been obvious to administer BVDU after administration of cytostatics during a recovery phase.

The Examiner is respectfully reminded that the claims are directed to administering a 5-substituted nucleoside comprising (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), salt, prodrug or mixture thereof, the administering being without administration of a cytostatic, during a recovery phase *after* a cytostatic chemotherapy cycle.

It is respectfully submitted that the Fahrig Abstract actually teaches away from the present invention. This is so because the Fahrig Abstract only discloses the *combination* of a 5' substituted nucleoside and a cytostatic. The Office Action provides no teaching or suggestion why one of ordinary skill in the art would be motivated to administer the 5' substituted

nucleoside without a cytostatic, during a recovery phase. Indeed, to infer that a disclosure to administer a combination suggests separate administration of a single component would be to eviscerate the entire meaning of the document. The Fahrig Abstract does not even make administration solely of a 5' substitute nucleoside obvious to try, since that would completely change the meaning of the Abstract. Accordingly, it is respectfully submitted that the Office Action does not establish a *prima facie* case of obviousness. On this basis alone, the rejection should be withdrawn.

In any event, it can be seen from the literal English translation of WO 96/23506 that the document teaches away even more strongly than presented above. In this regard, it is noted that the Office Action cites to the English abstract of the German language document WO 96/23506 in making the rejection. On October 14, 1997, PCT/DE96/00169 (which published as WO 96/23506) entered the U.S. national phase as Application No. 08/875,491, including a literal English translation of the International Application. A copy of the literal English translation that was filed is attached hereto for the Examiner's review, and will be referred to in the following discussion of WO 96/23506.[1]

A can be seen from the English translation, WO 96/23506 does not teach or suggest the recited method for at least the following reasons. WO 96/23506 theorizes that multi-drug resistance is attributed to gene amplification in cancer cells resulting in formation of protective proteins that "serve to shuttle toxins out of the cell." See English translation at page 1, lines 16-26. WO 96/23506 theorizes that 5' nucleosides such as BVDU prevent or attenuate

[1] The English translation is submitted in response to an issue raised in the Office Action. Thus, this document is submitted as evidence directed to an issue of patentability raised in an Office action. Accordingly, payment of a fee should not be necessary for consideration of this document. See M.P.E.P. §609C(3). However, if any fee is believed to be necessary for consideration of this document, this should be considered express authorization to charge appropriate fees to Deposit Account No. 19-0089.

these carcinogen-induced gene amplifications. See English translation at page 5, lines 6-16. It is respectfully submitted that one of skill in the art would understand these statements taken together to mean that the 5' nucleoside prevents or attenuates the "toxin shuttle" thereby leading to higher levels of the cytotoxic agent within the cancer cell, with increased probability of lethal effect. It is believed that this is why WO 96/23506 states that "it is proposed according to the invention to prevent or reduce resistance formation by simultaneous administration of 5' substituted nucleosides and a cytostatic agent." See English translation at page 5, lines 6-9. As disclosed in WO 96/23506, it would appear that one of skill in the art would expect the 5' substituted nucleoside to be effective only when it is present simultaneously with the cytotoxic agent.

As a result, WO 96/23506 discloses to those of skill in the art that administration of a 5' substituted nucleoside during a recovery phase would be ineffective. Therefore, as seen from the English translation, WO 96/23506 actually teaches away from administering a 5' substituted nucleoside during a recovery phase. By teaching away from the present invention, the present invention is unobvious over the Fahrig Abstract, as placed into clearer context in its English translation.

Even if the Office Action had established a *prima facie* case of obviousness (which Applicants maintain is not the case), the present application contains sufficient unexpected results to overcome the rejection. The Federal Circuit has stated that "unexpected results may be sufficient to rebut a *prima facie* case of obviousness." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed.Cir.2006); see also *In re De Blauwe*, 736 F.2d 699, 706 n. 8 (Fed.Cir.1984) ("A proper showing of unexpected results will rebut a prima facie case of obviousness."). "The basic principle behind this [rule] is straightforward — that which would have been surprising to a

person of ordinary skill in a particular art would not have been obvious." In re Mayne, 104 F.3d 1339, 1343 (Fed.Cir.1997).

The present application presents the surprising discovery that administration of a 5' substituted nucleoside during a recovery phase unexpectedly provides better chemotherapeutic results than where there is no such administration during the recovery phase. See Paragraph **[0014]** and **[0016]** - **[0019]** of the published application. These results are especially surprising in view of the theory presented in WO 96/23506, which would have suggested that administration of a 5' nucleoside during a recovery phase would be ineffective.

Accordingly, the present application provides sufficient unexpected results to overcome a *prima facie* case of obviousness, had the Office Action established such a rejection (which Applicants maintain is not the case).

For at least the above reasons, neither the Fahrig Abstract, nor WO 96/23506 (of which the Fahrig Abstract is part) teaches or suggests administering a 5' nucleoside (e.g., BVDU) during a recovery phase after a cytostatic chemotherapy cycle. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the obviousness rejection of claims 8-12, 16 and 17.

Conclusion

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention. Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested.

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully submitted,
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